Drug Substance(s)	AZD2171	**SYNOPSIS**	(For national authority use only)
Study Code	D8480C00019		
Date	26 March 2007		

Open, Non-randomised, Single Centre Pharmacokinetic and Mass Balance Study of Orally Administered [^{14}C]-AZD2171 (RECENTIN™) in Patients with Solid Metastatic Tumours

Study dates		**Phase of development**
First patient enrolled	9 November 2005	Clinical pharmacology (I)
Last patient enrolled	9 February 2006	

Objectives

The primary objective of the study was to determine the rates and routes of excretion of ^{14}C radiolabelled AZD2171 (RECENTIN™) in patients by assessment of concentrations of total ^{14}C radioactivity and AZD2171 in plasma, and concentrations of total radioactivity in urine and faeces.

The secondary objectives of the study were:

1. To characterise the metabolism of [^{14}C]-AZD2171 by assessment of metabolic profiles of selected plasma and excreta samples.

2. To calculate the pharmacokinetic (PK) parameters of [^{14}C]-AZD2171 in plasma and PK parameters of total plasma and whole blood radioactivity [a].

[a] The wording of this secondary objective was changed from that in the Clinical Study Protocol to reflect that the PK parameters in whole blood radioactivity were also determined during the study (please refer to changes to the planned analysis in Table 8).

3. To compare disposition of [^{14}C]-AZD2171 in plasma to whole blood.

4. To evaluate the safety and tolerability of once-daily oral doses of AZD2171 by assessment of adverse events (AEs), laboratory findings and vital signs.

5. To make a preliminary evaluation of clinical response as measured by objective tumour response rates.

The exploratory objectives of the study were:

1. To assess the reproducibility of dynamic contrast enhanced computed tomography (DCE-CT) vascular parameters.

2. To assess the effect of AZD2171 on tumour vasculature using DCE-CT.

Study design

This was an open, non randomised, radiolabelled, single centre study designed to determine the rates and routes of elimination of [^{14}C]-AZD2171 and its metabolites in patients. Each patient received a single oral 45 mg dose of [^{14}C]-AZD2171 and samples were collected to determine the total radioactivity of [^{14}C]-AZD2171 concentration in plasma as well as measurements of total radioactivity of [^{14}C]-AZD2171 and its metabolites in faeces and urine. Patients remained as in-patients at the hospital for up to 7 days following receipt of dose when samples of blood, urine and faeces were collected. Once ≥90% of the radiolabelled dose of [^{14}C]-AZD2171 was recovered or there was ≤3 x background in the urine and faeces samples, patients could continue treatment with once daily, unlabelled oral AZD2171 30 mg tablets if they were free from intolerable toxicity and were, in the investigator's opinion, able to continue treatment with AZD2171.

Target patient population and sample size

A total of 6 patients with solid metastatic tumours were to be recruited. **Key inclusion criteria:** histologically confirmed metastatic tumour, refractory to standard therapies; World Health Organisation (WHO) performance status 0-2; life expectancy of more than 12 weeks; one or more measurable lesions at least 25 mm in the longest diameter by spiral CT scan required for perfusion assessment using DCE-CT; and patients had to have an artery within the DCE-CT field of view required for estimating vascular parameters. **Key exclusion criteria:** radiotherapy within 4 weeks before the start of study treatment; chemotherapy within 4 weeks before the start of study treatment; inadequate bone marrow reserve as demonstrated by an absolute neutrophil count ≤1.5 x 10^9/L or platelet count ≤100 x 10^9/L or haemoglobin

<8 g/dL; ALT or AST ≥2.5 x upper limit of the reference range (ULRR) (if liver metastases were present, ALT or AST > 5x ULRR); serum bilirubin ≥ 1.5 x ULRR; creatinine clearance of ≤50mL/min calculated by Cockroft-Gault; mean QTc with Bazetts correction >470msec in screening ECG or history of familial long QT syndrome; patients with a history of poorly controlled hypertension with resting blood pressure (BP) >150/100 in the presence or absence of a stable regimen of hypertensive therapy; and history or evidence of any medical condition that might have affected gastrointestinal function.

Investigational product: dosage, mode of administration and batch numbers

A single, oral 45 mg dose of [^{14}C]-AZD2171 (100 μCi, 3.7 MBq; batch numbers: P/4126/08, P/4126/09 and P/4126/10) in a solution with 240 mL of purified water was administered on Day 1, in the morning following an overnight fast. Patients could continue to receive once-daily oral dosing with unlabelled AZD2171 30 mg (15 mg beige film coated tablets; batch numbers: P/4911/11 and P/4911/25).

Duration of treatment

Following receipt of a single oral 45 mg dose of [^{14}C]-AZD2171 (100μCi 3.7MBq), patients remained resident in the hospital for at least 7 days. Samples of blood, urine and faeces were collected for up to 7 days in order to ensure adequate recovery of the dose from all routes of elimination (eg, ≤3 x background radioactivity in the urine and faeces or greater than or recovery of ≥90% of total radioactivity). If adequate dose recovery had not been achieved by Day 7, patients were protocolled to return to the clinic on a weekly basis (up to an additional 21 days) until such time that the radiolabelled dose had been adequately recovered. In practice, only 1 patient (E0001998) had to return to the clinic after Day 7.

From Visit 3 (Day 10 onwards), patients could commence once-daily oral dosing with unlabelled AZD2171 30 mg (2 x 15 mg AZD2171 tablets); provided there was ≤3 x background radioactivity in the urine and faeces or if ≥90% of total radioactivity had been recovered.

Patients could continue to receive treatment if they were free from intolerable toxicity and in the investigator's opinion were receiving some benefit from treatment with AZD2171.

Variables

- **Pharmacokinetic**

  The plasma concentration of total radioactivity

  The whole blood concentration of total radioactivity

  The plasma concentrations of AZD2171

  The ratio of whole blood to plasma total radioactivity concentrations at individual time points

The percentage of radioactivity excreted in the urine and faeces

The ratio of AZD2171 plasma concentration to total plasma radioactivity

Derived PK parameters of AZD2171, AUC, $AUC_{(0-t)}$, $t_{½\lambda z}$, MRT, CL_R (AZD2171 only [a]) and CL/F (AZD2171 only [a])

[a] If a metabolites(s) is formed only CL_R and CL/F for unchanged AZD2171 can be calculated.

Pharmacokinetic parameters of total plasma and whole blood radioactivity: C_{max}, t_{max}

The cumulative percentage of the radioactive dose recovered in the urine and faeces by the end of each collection period.

- **Pharmacodynamic**

  DCE-CT imaging variables: the perfusion (mL/min/100 g), permeability surface (PS) product (mL/min/100 g), mean transit time (MTT, sec), positive enhancement integral (PEI, HUsec), blood volume (mL/100 g) and qualitative assessment of change in intensity, extent and pattern of contrast enhancement. Also, the within patient standard deviation of the 2 baseline values for each of the DCE-CT imaging variables

- **Efficacy**

  Objective tumour response assessed by RECIST criteria.

- **Safety**

  Blood Pressure (BP), Heart Rate (HR), ECG, Clinical Chemistry, Urinalysis, Haematology, AEs and Physical Examination.

Statistical methods

No formal statistical analysis was performed on the pharmacokinetic, efficacy or safety data from this study. However, a statistical analysis of the sources of variability in the DCE-CT data was performed and is detailed in Appendix 12.1.9.

Patient population

The key findings from the evaluation of the study population are as follows:

- A total of 6 patients were enrolled into this study at a single centre in the United Kingdom; the first patient was enrolled on 9 November 2005 and the last patient was enrolled on 9 February 2006.

- All 6 patients enrolled in the study received radiolabelled [^{14}C]-AZD2171 45 mg, and continued into the once-daily dosing part of the study where they received unlabeled AZD2171 at a dose of 30 mg. At the time of the database lock

(31 July 2006), 5 patients had permanently discontinued and 1 was still ongoing in the study.

- Five of the 6 patients were male and the median age of the patient population was 55.5 years (range: 38 to 68 years). The majority of patients (5 of 6) were Caucasian.

- The disease characteristics of the study patients were consistent with an advanced cancer population; the majority (5 of 6) had WHO performance status of 1 (restricted activity) and the primary tumour had metastasised to multiple sites.

- A wide variety of concomitant medications were taken throughout the study, including drugs that could affect hypertension, but none of these was considered to have interfered with the PK or mass balance assessments performed during the study.

Summary of pharmacokinetic results

The key findings from the evaluation of the AZD2171 PK profile are as follows:

- In 5 of the 6 patients enrolled in this study, the amount of radioactivity recovered in the urine and faeces samples within 168-hours post dosing ranged from 84.8 to 93.0% with the majority of the radioactivity recovered in the first 72 hours following dosing. In one patient, where no faeces were obtained for 3 days, the radioactivity recovered in urine and faeces was only 34.1% over the first 168-hours post dosing.

- In all 6 patients, the majority of the radioactivity was excreted in the faeces (arithmetic mean of 58.8%) with an arithmetic mean of 20.8% being excreted in the urine.

- A comparison of the arithmetic means of the ratios of whole blood to plasma radioactivity and plasma radioactivity to AZD2171 plasma concentrations following a single administration of [^{14}C]-AZD2171 supports the following:

  - that the radioactivity in whole blood is confined to plasma

  - the plasma concentrations of AZD2171 does not account for all AZD2171 drug-related substance in the plasma.

- Following a single dose of [^{14}C]-AZD2171, AZD2171 plasma concentrations reached their maximal value (t_{max}) from 2.0 to 6.0 hours post dosing with an overall median value of 3.6 hours. After attaining C_{max}, the plasma concentration of unchanged AZD2171 declined in an apparent biexponential manner with a $t_{½\lambda z}$ ranging from 14.9 to 44.7 hours with an overall arithmetic mean ± standard deviation value of 23.3 ± 10.7 hours.

- The median t_{max} for whole blood radioactivity of 3.0 hours was similar to the t_{max} for plasma total radioactivity of 3.5 hours. The geometric mean plasma radioactivity in terms of a C_{max} of 224 ng.quiv/g was higher than the C_{max} of whole blood radioactivity of 150 ng.quiv/g.

- The profiles of radioactive material in plasma and faeces showed 2 predominant regions. The smaller of these was assumed by co elution to be unchanged AZD2171, whilst the larger region eluted close to AZD2171, but was more polar.

- Very complex profiles were obtained for radioactive material in urine. A small component co-eluted with AZD2171, which confirmed that the proportion of dose excreted in urine as unchanged AZD2171 was low. Otherwise, the majority of components in urine were more polar than AZD2171.

Summary of pharmacodynamic results

The key findings from the evaluation of AZD2171 pharmacodynamics are as follows:

- DCE-CT imaging variables were assessed in order to determine the effect of AZD2171 on the tumour vasculature. DCE-CT data from this study provide some evidence of reductions in DCE-CT parameters post treatment, in particular for perfusion, PS product and PEI.

- Overall, the within-patient component of variability was generally low for all the DCE-CT parameters measured. The variability data show the inter-patient component of variability is consistently larger than the intra-patient component. The overall component of variability was largest for the PS product parameter, whilst the lowest variability was observed for the MTT parameter.

Summary of efficacy results

The key findings from the evaluation of AZD2171 efficacy are as follows:

- Data from an objective tumour response evaluation conducted according to RECIST criteria showed no patient experienced a CR or PR during this study.

- Three of the 6 patients had a best response of SD, including 1 patient with the SD sub-category of confirmed minor response, and 2 patients with the sub-category of no confirmed reductions from baseline ≥10%.

- Of the remaining 3 patients, 2 had best responses of PD and 1 was non-evaluable for response.

Summary of safety results

The key findings from the evaluation of AZD2171 safety are as follows:

- Six patients received a 45 mg single oral dose of [^{14}C]-AZD2171 1 mg/mL solution, containing nominally 100µCi 3.7 MBq. Of these patients, all went on to receive once-daily treatment with unlabelled AZD2171 30 mg. During the once-daily dosing part of the study, the highest actual exposure to AZD2171 30 mg was 171 days, while the lowest was 64 days. One of the 6 patients had a dose interruption during once-daily dosing.

- Three patients had at least one AE during the radiolabelled [^{14}C]-AZD2171 45 mg part of the study.

- All 6 patients experienced at least one AE during daily dosing with unlabelled AZD2171 30 mg.

- Diarrhoea (5 of 6 patients), hypertension (3 of 6 patients), constipation, fatigue, dyspnoea, and neck pain (2 of 6 patients) were the only AEs to occur in more than 1 patient. Hypertension (3 of 6 patients) and diarrhoea (2 of 6 patients) were the most commonly reported AEs considered by the investigator to be related to study treatment.

- Overall, there was 1 SAE, 1 AE leading to discontinuation of treatment with investigational product (IP), and 1 AE leading to death during the study. Patient E0001996 accounted for each of these events. The primary cause of death was given as an AE of chest infection with secondary cause of death considered to be due to metastatic dematofibrosarcoma protuberans.

- No other significant AEs (OAEs) were identified during the conduct of this study.

- There were no clinically significant trends in haematology, clinical chemistry or urinalysis parameters during the study.

- There were no clinically relevant trends in ECG observations, vital signs or physical findings.